CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567

CHEMISTRY REVIEW(S)

NDA 21-567

Reyataz (atazanavir capsules)

Bristol-Myers Squibb

Dan Boring, R.Ph., Ph.D.
Division of Anti-viral Drug Products, HFD-530

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-567

2. REVIEW #: 1

3. REVIEW DATE: 4/1/03

4. REVIEWER: Dan Boring, R.Ph., Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-567	12/20/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol-Myers Squibb
Address:	5 Research Parkway Wallingford, CT 06492
Representative:	Dr. Lois Sechler
Telephone:	(609) 818-5306

CHEMISTRY REVIEW

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Reyataz™
b) Non-proprietary Name: (USAN): Atazanavir Sulfate
c) Code Name/# (ONDC only): BMS-232632
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-retroviral

11. DOSAGE FORM: immediate-release capsule

12. STRENGTH/POTENCY: 100, 150, 200 mg

13. ROUTE OF ADMINISTRATION: oral

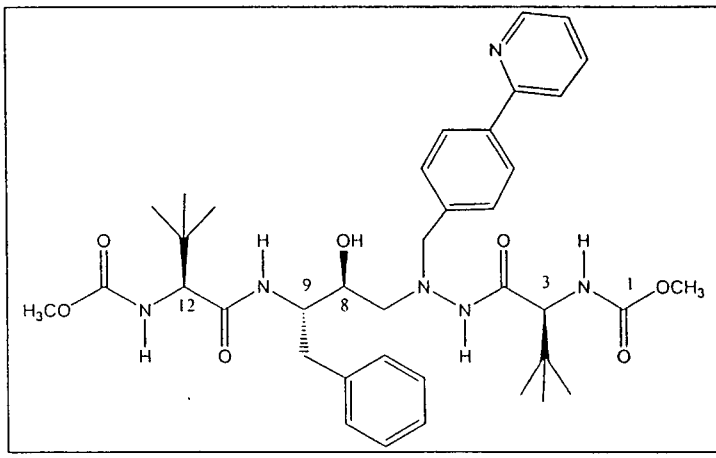
14. Rx/OTC DISPENSED: __X__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



(3S,8S,9S,12S)-3,12-bis(1,1,-dimethylethyl)-8-hydroxy-4,11-dioxo-9-phenylmethyl-6-[[4-(2-pyridinyl)phenyl]methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester, sulfate (1:1)

$C_{38}H_{52}N_6O_7 \cdot H_2SO_4$

$M_r = 802.9$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	4	Adequate		
[redacted]	II	[redacted]	[redacted]	4	Adequate		
[redacted]	II	[redacted]	[redacted]	4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	[redacted]	Pre-clinical and clinical development

18. STATUS:

None requested by chemistry reviewer

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology			

The Chemistry Review for NDA 21-567

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is may be approved, as amended. There are a few minor informational issues outstanding that will not affect the approval of this application.

B. Post-Marketing Phase 4 Commitments, Agreements, and/or Risk Management Steps, if Recommendation is for Approval.

1. Develop and add a test for optical rotation with numerical acceptance criteria to the drug substance specification

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance USAN is atazanavir sulfate. It is a crystalline material with low water solubility a neutral pH. It is most soluble in acidic media and least soluble in basic media. Studies indicate that the drug substance may exist in several morphic forms, solvates and hydrates. However the commercial synthetic process yields an unsolvated, single morphic form (Form A). The drug substance has four chiral centers, therefore 16 stereo-isomers are theoretically possible. The specific enantiomer of the drug substance is prepared and controlled through a stringent stereochemical specification of starting materials, intermediates and final substance and a stereospecific synthetic method. The analytical methods developed are able to distinguish many of the possible enantiomeric and diastereomeric impurities that could arise in starting materials and final product. The drug substance particle size is tightly controlled to ensure consistent processing and bioavailability. The drug substance is a relatively pure substance and has no individual impurity (identified or unidentified) at greater than 0.1% w/w.

The drug substance specification is generally adequate, however it was recommended that another regulatory method be added for routine identification and that a test by optical rotation be added to the specification to further ensure enantiomeric identity. It was also recommended that the water content test have acceptance criteria and that the limits for the residual solvents be tightened from respectively. The analytical methods are all satisfactory.

The recommended storage condition for Atazanavir Sulfate is below 30 °C, protected from moisture, with a desiccant packet between the inner and the outer bag. Atazanavir Sulfate has been assigned a retest period of one year. None of the stability indicating parameters (residual solvents, X-ray diffraction, appearance, purity, water content and impurities) changed significantly when stored at 25°C/60%RH.

The drug product is an immediate-release, oral, hard gelatin capsule available in — 100, 150 and 200-mg strengths packaged in 60-count bottles. The formulation consists of the drug substance, lactose, crospovidone and magnesium stearate. The product is manufactured by a process with water as the solvent followed by . A common blend is used to prepare all four strengths of drug product and there are no re-processing operations. The packaging and labeling processes are satisfactory.

The drug product specification is generally adequate. However, it was recommended that a second regulatory identity test be added. Also, it was recommended that the dissolution acceptance criteria be tightened from Q= in 30 minutes to Q= in 20 minutes. The proposed analytical methods are all satisfactory.

B. Description of How the Drug Product is Intended to be Used

Reyataz™ (atazanavir) capsules contain atazanavir sulfate, an azapeptide protease inhibitor. Its indication is for treatment of HIV infection in combination with ritonavir. The product is available in — 100, 150 and 200-mg strengths in 60-count bottles. The recommended adult daily dose is one 200 mg capsule twice daily for a total daily dose of 400 mg. The 60-count bottle is intended to provide one month of medication.

The stability studies support an expiration period of 24 months in the commercial packaging when stored at controlled room temperature. The stability studies used a bracketing design where 30 and 90-count bottles of each strength were placed into the long-term and accelerated stability studies. The 30-count bottle for all strengths was the least protective packaging, however none of the critical stability indicating parameters (assay, impurities and dissolution) changed significantly through 24-months at 25°C/60%RH storage. but less so at the intermediate 30°C/60% condition and it was recommended that testing at the 30°C/60%RH condition be added to the post-approval stability protocol.

C. Basis for Approval, Approvable or Not-Approval Recommendation

The NDA submission and amendment ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Reyataz™ (atazanavir) capsules.

Five manufacturing, packaging and testing facilities were submitted for prior-approval assessment.

Bristol-Myers Squibb Manufacturing Company
Road #2, KM 56.4
Barceloneta, Puerto Rico 00617

BMS Pharmaceutical Research Institute
St. Nazaire, France

Bristol-Myers Squibb Company
2400 West Lloyd Expressway
Evansville, Indiana 47721

Bristol-Myers Squibb Company
4601 Highway 62 East
Mt. Vernon, Indiana 47620

As of June 11, 2003, four have been found acceptable. The inspection of the St. Nazaire, France site was carried out June 2 - 6, 2003, and the results are not yet evaluated by CDER's Office of Compliance. Since the French site conducted stability studies on the drug substance and drug product only used in clinical trials, this NDA can be approved even if the French site is judged to be unacceptable.

It was recommend that the established name of this product be expressed on the immediate container label and carton in terms of atazanavir free-base. For example:

(atazanavir capsules)
or
(atazanavir)capsules
x mg

where x = — 100, 150 or 200 mg

with a statement provided on the immediate container label such as:

Each capsule contains x mg of atazanavir as the sulfate salt. The applicant committed to revise the labeling at the next label printing to conform to this recommendation.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

CHEMISTRY REVIEW

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21567/000** Priority: **1P** Org Code: **530**
Stamp: **20-DEC-2002** Regulatory Due: **20-JUN-2003** Action Goal: District Goal: **21-APR-2003**
Applicant: **BRISTOL MYERS SQUIBB CO**
5 RESEARCH PKY
WALLINGFORD, CT 06492
Brand Name: **ATAZANAVIR CAPSULES**
Established Name:
Generic Name: **ATAZANAVIR**
Dosage Form: **CAP (CAPSULE)**
Strength: **100 MG, 150 MG, 200 MG**

FDA Contacts:			
	V. REDDY	**(HFD-530)**	**301-827-2335 , Project Manager**
	D. BORING	**(HFD-530)**	**301-827-2396 , Review Chemist**
	S. MILLER	**(HFD-530)**	**301-827-2392 , Team Leader**

Overall Recommendation:

Establishment: **2623241** DMF No:
BRISTOL MYERS BARCELONETA IN AADA No:
RD 2 KM 56.4
BARCELONETA, PR 00617

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-MAY-2003**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
DRUG SUBSTANCE OTHER TESTER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment: **1819504** DMF No:
BRISTOL MYERS SQUIBB CO AADA No:
2400 WEST LLOYD EXPY
EVANSVILLE, IN 477210001

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-APR-2003**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: **1825662** DMF No:
BRISTOL MYERS SQUIBB CO AADA No:
HWY 62 WEST BLDG 122
MOUNT VERNON, IN 47620

Profile: **CHG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE PACKAGER**

03-JUN-2003

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Milestone Date: **01-APR-2003**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: **BRISTOL MYERS SQUIBB PHARMAC**
ROUTE DE SAINT ANDRE DE EAUX
SAINT NAZAIRE, , FR 44600

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **11-APR-2003**

Responsibilities: **DRUG SUBSTANCE STABILITY TESTER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **09-APR-2003**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dan Boring
6/11/03 04:47:42 PM
CHEMIST

Stephen Paul Miller
6/12/03 02:58:59 PM
CHEMIST
Approval recommended from CMC perspective